

Remarks

In view of the above amendments and the following remarks, reconsideration of the outstanding office action is respectfully requested.

The primary developmental events of plants originate from the shoot apical meristem (SAM). The shoot apical meristem is responsible for the formation of vegetative organs such as leaves, and may undergo a phase change to form the inflorescence or floral meristem. Many of these events are controlled at the molecular level by transcription factors. Transcription factors (TFs) are proteins that act as developmental switches by binding to the DNA (or to other proteins that bind to the DNA) of specific target genes to modulate their expression. An important family of TFs involved in regulating the developmental events in apical meristems is the *knox* (knotted-like homeobox) gene family. *Knox* genes have been isolated from several plant species and can be divided into two classes based on expression patterns and sequence similarity. Class I *knox* genes have high similarity to the *kn1* homeodomain and generally have a meristem-specific mRNA expression pattern. Class II *knox* genes usually have a more widespread expression pattern.

Knox genes belong to the group of TFs known as the TALE superclass. These TFs are distinguished by a very high level of sequence conservation in the DNA-binding region, designated the homeodomain, and consisting of three α -helices similar to the bacterial helix-loop-helix motif. The third helix, the recognition helix, is involved in DNA-binding. TALE TFs contain a three amino acid loop extension (TALE), proline-tyrosine-proline, between helices I and II in the homeodomain, that has been implicated in protein interactions. There are numerous TFs from plants and animals in the TALE superclass and the two main groups in plants are the KNOX and BEL types. Related genes in animal systems play an important role in regulating gene expression.

Expression patterns and functional analysis of mutations support the involvement of *knox* genes in specific developmental processes of the shoot apical meristem. *Kn1* from maize, the first plant homeobox gene to be discovered, is involved in maintenance of the shoot apical meristem and is implicated in the switch from indeterminate to determinate cell fates. Transcripts of *kn1* in maize, *OSH1* in rice, and *NTH15* in tobacco were localized by *in situ* hybridization to undifferentiated cells of the corpus and the developing stem, but were not detected in the tunica or leaf primordia. Overexpression of *kn1* in Arabidopsis and in tobacco resulted in plants with altered leaf morphologies including lobed, wrinkled or curved leaves with shortened petioles and decreased elongation of veins.

Plants were reduced in size and showed a loss of apical dominance. In plants with a severe phenotype, ectopic meristems formed near the veins of leaves indicating a reversion of cell fate back to the indeterminate state. Overexpression of *OSH1* or *NTH15* in tobacco resulted in altered morphologies similar to the 35S-*kn1* phenotype.

Alterations in leaf and flower morphology in 35S-*NTH15* or *OSH1* transgenic tobacco were accompanied by changes in hormone levels. Whereas levels of all the hormones measured were changed slightly, both gibberellin and cytokinin levels were dramatically altered. RNA blot analysis revealed that the accumulation of GA 20-oxidase1 mRNA was reduced several fold in transgenic plants. A KNOX protein of tobacco binds to specific elements in regulatory regions of the GA 20-oxidase1 gene of tobacco to repress its activity. GA 20-oxidase is a key enzyme in the GA biosynthetic pathway necessary for the production of the physiologically inactive GA₂₀ precursor of active GA₁. GA₁ and other active GA isoforms are important regulators of stem elongation, the orientation of cell division, the inhibition of tuberization, flowering time, and fruit development.

Another plant homeobox gene family that is closely related to the *knox* genes is the BEL (BELL) family. BEL TFs have been implicated in flower and fruit development. Genetic analysis of *BEL1* in *Arabidopsis* showed that expression of this TF regulated the development of ovule integuments and overlaps the expression of *AGAMOUS*. In *COP1* mutants, the photoinduced expression of *ATH1*, another BEL TF of *Arabidopsis*, was elevated, indicating a possible role in the signal transduction pathway downstream of *COP1*.

Plants must maintain a great deal of flexibility during development to respond to environmental and developmental cues. Responses to these signals, which include day length, light quality or quantity, temperature, nutrient and hormone levels, are coordinated within the meristem. In potato, there is a specialized vegetative meristem called the stolon meristem that develops as a horizontal stem and under inductive conditions will form the potato tuber. Potato offers an excellent model system for examining how vegetative meristems respond to external and internal factors to control development at the molecular level. In model tuberization systems, synchronous tuber formation occurs under inductive conditions and shoot or stolon formation occurs under noninductive conditions. The cellular and biochemical processes that occur in these model systems have been examined extensively. In addition to being good systems to examine integration of signals at the meristem, understanding the molecular processes controlling tuberization in potato is important. Potato is the fourth largest crop produced in the world, ranking after maize, rice,

and wheat, and is a major nutritional source in many countries; therefore, research focusing on the process of tuber initiation and development is very important.

Tuber formation in potatoes (*Solanum tuberosum* L.) is a complex developmental process that requires the interaction of environmental, biochemical, and genetic factors. Several important biological processes like carbon partitioning, signal transduction, and meristem determination are involved. Under conditions of a short-day photoperiod and cool temperature, a transmissible signal is activated that initiates cell division and expansion and a change in the orientation of cell growth in the subapical region of the stolon tip. In this signal transduction pathway, perception of the appropriate environmental cues occurs in leaves and is mediated by phytochrome and gibberellins. Tuber development at the stolon tip is comprised of biochemical and morphological processes. Both are controlled by differential gene expression with most of the work focusing on the biochemical processes, including starch synthesis and storage protein accumulation.

Much less is known about the morphological controls of tuberization, although it is clear that phytohormones play a prominent role. Gibberellins (GA), in particular, play an important role in regulating tuber development. High levels of GA are correlated with the inhibition of tuberization, whereas low levels are associated with the induction of tuber formation. Specific genes, such as lipoxygenases and MADS box genes that are involved in regulating tuber formation have been identified.

At the time of filing, three independent research groups had recently confirmed that BEL-like TFs interact via protein binding with their respective *knox*-types in three separate species, but there were no published reports on the function of this interaction. Moreover, nothing was known about the role of either KNOX or the BEL TFs in the regulation of development of tuberous plants, such as potato.

The present invention is directed to overcoming these and other deficiencies in the art.

Claims 26-42 have been canceled without prejudice as being directed to non-elected subject matter. Applicants reserve the right to pursue the non-elected subject matter in one or more related applications. Claims 1, 3, 4, 11, 14, 15, 21, 22, 43, 45, 46, 48, 50, 52, 53, and 55 have been amended, and new claims 57-68 have been added, so that claims 1-25 and 43-68 are now pending.

The objection to claims 2-6, 13-16, 20-23, 44-47, and 51-54 for being drawn to non-elected inventions is respectfully traversed in view of the above amendments and the following remarks.

In the Response to Restriction Requirement (dated July 7, 2005), applicants elected nucleotide sequence SEQ ID NO:1 (*StBEL-5 gene*) and its corresponding encoded amino acid sequence SEQ ID NO:2 (*StBEL-5 protein*). Therefore, it is applicants' understanding that the basis for this objection is the recitation in the objected to claims of non-elected sequences SEQ ID NOs:3-14. For the reasons discussed below, applicants respectfully submit that it is reasonable to maintain these non-elected sequences for prosecution in the present application.

Pursuant to MPEP § 803.04, “[i]t has been determined that normally ten sequences constitute a reasonable number for examination purposes. Accordingly, in most cases, up to *ten independent and distinct nucleotide sequences* will be examined in a single application without restriction” (at 800-10, Rev. 3, August 2005) (emphasis added). Under this standard, applicants respectfully request that the Examiner withdraw the restriction requirement as to SEQ ID NOs:3-14. In the present application, as shown in **Table I** below, only 6 of the 12 non-elected sequences are nucleotide sequences; the remaining 6 sequences are the amino acid sequences of the proteins encoded by the non-elected nucleotide sequences.

Table I
**Nucleotide and Amino Acid Sequences Corresponding to
Non-Elected BEL Transcription Factors**

BEL Transcription Factor	Nucleotide Sequence	Amino Acid Sequence
StBEL-11	SEQ ID NO:3	SEQ ID NO:4
StBEL-13	SEQ ID NO:5	SEQ ID NO:6
StBEL-14	SEQ ID NO:7	SEQ ID NO:8
StBEL-22	SEQ ID NO:9	SEQ ID NO:10
StBEL-29	SEQ ID NO:11	SEQ ID NO:12
StBEL-30	SEQ ID NO:13	SEQ ID NO:14

Therefore, pursuant to MPEP § 803.04, applicants respectfully request that the Examiner withdraw the restriction requirement as to the six remaining nucleotide sequences of SEQ ID NOs:3, 5, 7, 9, 11, and 13, and their corresponding encoded amino acid sequences of SEQ ID NOs:4, 6, 8, 10, 12, and 14.

The objection to the specification for containing an embedded hyperlink and/or other form of browser-executable code is respectfully traversed in view of the above amendments to paragraph [0035] of the specification. No new matter has been added by this amendment.

The rejection of claims 48 and 55 under 35 U.S.C. § 112 (2nd para.) for indefiniteness is respectfully traversed in view of the above amendments to claims 48 and 55.

The rejection of claims 1, 3, 4, 7-12, 14, 15, 17-19, 21, 22, 24, 25, 43, 45, 46, 48-50, 52, 53, 55, and 56 under 35 U.S.C. § 112 (1st para.) for lack of adequate written descriptive support is respectfully traversed in view of the above amendments and the following remarks.

The U.S. Patent and Trademark Office (“USPTO”) alleges that the claimed invention lacks written descriptive support, because the specification (i) does not identify essential regions that are unique to StBEL-05 proteins encoded by SEQ ID NO:1; (ii) does not describe any polynucleotide sequences that encode any BEL transcription factor; (iii) does not describe any polynucleotide sequences that encode any BEL transcription factor that hybridizes to SEQ ID NO:1 under stringent conditions and encode a protein with the same activity and function as the StBEL-05 protein encoded by SEQ ID NO:1.

To support this rejection, the USPTO has taken the position that the specification fails to describe a representative number of polynucleotide sequences encoding an StBEL-05 protein falling within the scope of the claimed genus of polynucleotides which encode any BEL transcription factor, or encode any BEL transcription factor wherein the protein is at least 85% similar to any homeodomain region, a SKY box, a BELL domain, and a VSLTLGL-box in SEQ ID NO:2, or wherein the nucleic acid molecule hybridizes under stringent conditions to SEQ ID NO:1 (Office Action, at page 6). Instead, the USPTO asserts that the specification only describes a single cDNA sequence (i.e., SEQ ID NO:1). The USPTO also asserts that the specification fails to describe structural features common to the members of the claimed genus of polynucleotides. Thus, the USPTO asserts that the specification fails to meet either of the prongs of the two-prong test set forth in *University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 1569, 43 U.S.P.Q.2d 1398 (Fed. Cir. 1997). In addition, the USPTO states that, given the lack of description of the necessary elements essential for the StBell-05 protein, it remains unclear what features identify the StBell-05 protein (Office Action, at page 6). In view of the above amendments to the claims, applicants respectfully disagree with the USPTO’s conclusions, as set forth in more detail below.

Applicants first wish to point out that the BEL transcription factors of the rejected claims are limited to a *single* plant species, namely, to the *Solanum tuberosum* plant. Second, the only independent claim (i.e., claim 1) has been amended to include further limitations with regard to the claimed isolated nucleic acid molecule encoding the BEL transcription factor from *Solanum tuberosum*. In particular, claim 1 now recites that the isolated nucleic acid molecule:

- (a) comprises a nucleotide sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, and SEQ ID NO:13; or
- (b) comprises a nucleotide sequence that is at least 90% similar to a nucleotide sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, and SEQ ID NO:13, and that encodes a protein that comprises an amino acid sequence having a homeodomain region, a SKY box, a BELL domain, and a VSLTLGL-box that are at least 90% similar to the corresponding homeodomain regions, SKY boxes, BELL domains, and VSLTLGL-boxes in either SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, or SEQ ID NO:14 by basic BLAST using default parameters analysis; or
- (c) hybridizes to the nucleotide sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, or SEQ ID NO:13 under high stringency conditions characterized by hybridization in a buffer of 4-5X SSC/0.1% w/v SDS at 54°C for 1-3 hours and in 4X SSC at 65°C, followed by a washing in 0.1X SSC at 65°C for about one hour; or
- (d) encodes a protein or polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, and SEQ ID NO:14.

Therefore, as described in more detail below, applicants respectfully submit that these amendments obviate the grounds for this written description rejection.

The present specification describes *seven* BEL transcription factors (“TFs”) from *Solanum tuberosum*. Each of these BEL TFs is described in the specification (at pages 22-42) by its nucleotide sequence (SEQ ID NOs:1, 3, 5, 7, 9, 11, and 13) *and* its amino acid sequence (SEQ ID NOs:2, 4, 6, 8, 10, 12, and 14). In addition, the specification (at page 16,

lines 12-17; Example 26, at page 90, line 15 to page 91, line 15; and Figure 13A) identifies the following four amino acid domain regions as being characteristic of the claimed *Solanum tuberosum* BEL TFs: (i) a homeodomain region; (ii) a SKY box region; (iii) a BELL domain region; and (iv) a VSLTLGL-box region. Figure 13A is a schematic showing these four domain regions. Each of these domain regions is also described throughout the specification in more detail. For example, the specification teaches that “[t]he close match of all seven [of the BEL TFs] to the conserved homeodomain and the presence of proline-tyrosine-proline (P-Y-P) loop between helices I and II (Figure 13A) distinguish these novel proteins as BEL types in the TALE superclass” (at page 90, lines 29-32). The specification (at page 91, lines 3-5) further teaches that the homeodomain region is nearly identical among the seven BEL TFs (see Figure 13A, encompassing helices I, II, and III). The other domain regions are also described in the specification with more specificity to include the “amino-terminal SKY box consisting of 20 aa (from ser-207 to lys-226 in StBEL-05), the 120-aa domain starting at leu-272 of the StBEL-05 sequence, and the carboxy-terminal VSLTLGL-box (SEQ ID NO:15) beginning at val-620” (at page 91, lines 5-8). It is clear that making specific mention of the “StBEL-05” in the specification identifies StBEL-05 as a reference sequence, but does not limit the disclosure to just StBEL-05.

As amended or added, claims 1(b), 3, 14, 21, 45, 52, 58, 61, and 66 now include both nucleotide and amino acid sequence limitations (as already described fully above). In particular, the recited isolated nucleic acid molecule must have a nucleotide sequence that is “*at least 90% similar*” to one of the specifically described BEL TF nucleotides *and* also encode a protein “having a homeodomain region, a SKY box, a BELL domain, and a VSLTLGL-box that are *at least 90% similar* to the corresponding homeodomain regions, SKY boxes, BELL domains, and VSLTLGL-boxes in either SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, or SEQ ID NO:14 by basic BLAST using default parameters analysis” (emphasis added). Descriptive support for these limitations is provided in the specification at page 43, lines 5-10 and 29-32.

As amended or added, claims 1(c), 4, 15, 22, 46, 53, 59, 63, and 67 now recite “high stringency” hybridization conditions (noted above). Descriptive support for these high stringency conditions is provided in the specification at page 44, lines 15-18.

That the present application supports the claims is entirely consistent with the Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, ¶1, "Written Description" Requirement, 66 Fed. Reg. 1099 (Jan. 5, 2001) ("Written Description Guidelines"), because the present specification describes both "a representative number of species" and discloses "structural or other physical and/or chemical properties" (as well as a correlation between structural and functional properties).

The burden of establishing that an application lacks adequate written descriptive support falls on the USPTO. *See In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976) ("[T]he PTO has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims."). Applicants respectfully submit that, in view of the above amendments to the claims, the USPTO has not met its burden of presenting evidence as to why a skilled artisan would not recognize the present application as described in the claimed invention (as amended).

For the foregoing reasons, applicants respectfully submit that the instant invention was described in a manner which would convey to one skilled in the art that applicants had possession of the claimed invention at the time they filed the present application. Therefore, the rejection of claims 1, 3, 4, 7-12, 14, 15, 17-19, 21, 22, 24, 25, 43, 45, 46, 48-50, 52, 53, 55, and 56 under 35 U.S.C. § 112 (1st para.) for lack of adequate written descriptive support is improper and should be withdrawn.

The rejection of claims 1, 3, 4, 7-12, 14, 15, 17-19, 21, 22, 24, 25, 43, 45, 46, 48-50, 52, 53, 55, and 56 under 35 U.S.C. § 112 (1st para.) for lack of enablement is respectfully traversed in view of the above amendments and the following remarks.

The USPTO has acknowledged that the specification is enabling for "an isolated nucleic acid molecule of SEQ ID NO:1 encoding the polypeptide of SEQ ID NO:2, a DNA construct and expression vector comprising said isolated nucleic acid molecule; and host cell, transgenic plant, and transgenic plant seed transformed with the isolated nucleic acid molecule" (Office Action, at page 6). However, the USPTO has taken the position that the claims (as originally filed) were too broad to enable the skilled artisan to make and use the invention. The USPTO has also taken the position that the specification is not enabling for the claimed method of enhancing growth in a plant or method of regulating flowering in a plant comprising transforming a plant with SEQ ID NO:1 (Office Action, at page 7). As discussed previously (in regard to the written description rejection), the claims have been

amended to include limitations as to nucleotide and amino acid sequences, similarity, and hybridization conditions. Applicants assert that, in view of these amendments, the lack of enablement rejection, based on the grounds described in this paragraph, is improper and should be withdrawn.

Regarding claim 43, the USPTO asserts that the specification fails to enable a method of “enhancing growth” of plants. However, the USPTO acknowledges that the specification is enabling for “a method of increasing the growth rate of a plant, or increasing the number and size of potato tubers comprising transforming a plant with SEQ ID NO:1” (Office Action, at page 9). In view of the amendments to claim 43, applicants assert that this ground for rejection is improper and should be withdrawn.

Regarding claim 50, the USPTO asserts that the specification fails to disclose by way of example that the claimed invention has any effect or influence on flowering (Office Action, at page 9). It appears that the USPTO is requiring that examples be included in the specification in order to enable the claims. Applicants respectfully disagree that the enablement requirement of 35 U.S.C. § 112 (1st para.) requires that the specification include experimental examples regarding methods of use. Thus, applicants respectfully request that this ground for rejection be withdrawn, or that the Examiner further clarify whether evidence of flower regulation by overexpressing the StBEL TFs in a plant can be used to obviate this ground for rejection. If such evidence will be acceptable, applicants reserve the right to enter that evidence in its next response to rebut this ground for rejection.

The USPTO also asserts that the state of the art teaches that isolating DNA fragments using stringent hybridization conditions does not always select for DNA fragments whose contiguous nucleotide sequence is the same or nearly the same as the probe (Office Action, at page 9). To support this assertion, the USPTO cites to Fourgoux-Nicol et al., “Isolation of Rapeseed Genes Expressed Early and Specifically During Development of the Male Gametophyte,” *Plant Molec. Biol.* 40:857-872 (1999) (“Fourgoux-Nicol”). In particular, the USPTO describes Fourgoux-Nicol (at page 859, left col., 2nd para.) as teaching the isolation of a 674bp fragment using a 497bp probe incorporating stringent hybridization conditions comprising consecutive 30-minute rinses in 2X, 1X, and 0.1X SSC with 0.1% SDS at 65°C. The USPTO further asserts that Fourgoux-Nicol teaches that the probe and isolated DNA fragment had a number of sequence differences. However, applicants point out that the claims of the present invention have been amended to include “high stringency” conditions, namely, “hybridization in a buffer of 4-5X SSC/0.1% w/v SDS

at 54°C for 1-3 hours and in 4X SSC at 65°C, followed by a washing in 0.1X SSC at 65°C for about one hour" (see amended claims 1(c), 4, 15, 22, 46, 53 and new claims 59, 63, and 67). It is well known in the art that decreasing the time, increasing the temperature, and decreasing the salt concentration with respect to hybridization and washing conditions correlate to higher stringency conditions. The USPTO failed to describe the initial hybridization conditions described in Fourgoux-Nicol, but only described the washing conditions. In particular, Fourgoux-Nicol (at page 859, left column, 2nd paragraph) states that the initial hybridization was at "65°C in 6X SSC for 24 h." In contrast, the initial hybridization conditions recited in the amended and new claims are higher in regard to salt concentration and time of hybridization. Further, the final washing conditions of the present claims are more stringent in two of the categories (time and salt concentration) and equivalent in one category (temperature) compared to those of Fourgoux-Nicol. Thus, applicants assert that the USPTO has not carried its burden to show that the specification fails to enable the rejected claims reciting hybridization conditions.

The USPTO proffers additional bases for the lack of enablement rejection. For example, the USPTO states that the state-of-the-art is such that one of skill in the art cannot predict which nucleic acids that hybridize under stringent conditions to SEQ ID NO:1 will encode a protein with the same activity as a protein encoded by SEQ ID NO:1 (Office Action, at page 10). Applicants respectfully disagree that this broad statement applies to the claims as amended. The USPTO also asserts that the state-of-the-art teaches that transforming plants with homeobox transcription factors produces unexpected results (Office Action, at page 10). Applicants note that the USPTO's support for this is based on research using the *Arabidopsis* knotted1-like gene (KNAT1). Thus, applicants respectfully disagree that this ground for rejection is applicable to the claims, as amended and as newly added. The USPTO further asserts that applicants have not disclosed how one makes or isolates any of the sequences that are encompassed by applicants' "broad claims" (Office Action, at page 11, lines 1-2). Applicants assert that this basis for rejection is no longer correct or supportable in view of the amendments to the claims. The USPTO states that applicants have not taught which regions of the respective polynucleotides can be used to amplify any of said polynucleotides or which regions can be used as a probe to isolate any of said polynucleotide sequences. Applicants disagree that this ground for rejection is still valid in view of the amendments. Further, applicants respectfully submit that the skilled artisan has sufficient

guidance in the specification to make and use, without undue experimentation, the inventions now claimed.

Therefore, for all of the reasons described above, applicants respectfully submit that the rejection of claims 1, 3, 4, 7-12, 14, 15, 17-19, 21, 22, 24, 25, 43, 45, 46, 48-50, 52, 53, 55, and 56 under 35 U.S.C. § 112 (1st para.) for lack of enablement is improper and should be withdrawn.

The rejection of claim 11 under 35 U.S.C. § 101 as being directed to non-statutory subject matter is respectfully traversed in view of the above amendments to claim 11.

In view of all of the foregoing, applicants submit that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,



Andrew K. Gonsalves
Registration No. 48,145

Date: March 23, 2006

NIXON PEABODY LLP
Clinton Square, P.O. Box 31051
Rochester, New York 14603-1051
Telephone: (585) 263-1658
Facsimile: (585) 263-1600

CERTIFICATE OF MAILING OR TRANSMISSION [37 CFR 1.8(a)]

I hereby certify that this correspondence is being:

deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to: Mail Stop Amendment, Commissioner for Patents, P. O. Box 1450, Alexandria, VA 22313-1450

transmitted by facsimile on the date shown below to the United States Patent and Trademark Office at (703) _____.

March 23, 2006
Date



Signature

Jo Ann Whalen
Type or Print Name